REMARKS

I. Claims under Consideration

Claims 5, 6, 8-15, and 17 are pending in the application. Claim 6 and 15 were rejected under 35 U.S.C. § 101, claims 6, 9-12, and 14-15 were rejected under 35 U.S.C. § 112, second paragraph, claims 5-6, 8-15, and 17 were rejected under 35 U.S.C. § 112, first paragraph, and claims 5-6 and 8-15 were rejected under 35 U.S.C. § 102. Applicants address each of these rejections as follows.

II. Amendments

Applicants have canceled claims 9, 11, and 13 and have amended claims 5, 6, 8, 10, 12, 14, 15, and 17. The amendments to claims 5, 8, and 14 find support, for example, at page 2, lines 16-21, and page 3, lines 14-26, of the specification, and in canceled claims 9 and 11. Claim 14 also finds support, for example, at page 6, lines 25-28, of the specification. The amendment to claim 17 is supported by the specification, for example, at page 6, lines 2-7. Claims 6 and 15 have been amended, as suggested by the Office, to refer to isolated cells. In view of the cancellation of claims 9 and 11, the dependency of claims 10 and 12 has been amended.

New claims 18 and 19 have been added. Support for these claims may be found throughout the specification, for example, at page 6, line 25, to page 7, line 2. In addition, Applicants have amended the cross-reference to related applications to conform

to the requirements of 37 C.F.R. § 1.78. No new matter has been added by these amendments.

III. Objection to the Drawings

The Office objected to the quality of the drawings for Figures 1 and 4-9. Applicants have replaced original Figures 1 and 4-9 with corrected drawings for these figures. No new matter has been added by this amendment. Applicants submit that this basis for objection should be withdrawn.

IV. Rejections Under 35 U.S.C. § 101

Claims 6 and 15 were rejected under 35 U.S.C. § 101 for containing non-patentable subject matter. As suggested by the Office, claims 6 and 15 have been amended to refer to isolated cells. Applicants submit that the present claims, as amended, are free of this rejection.

V. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 6, 9-12, and 14-15 were rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. In particular, the Office objected to the recitation of the phrase "derived from" in claims 9-12, the Office asserted that claim 14 does not further limit the claim from which it depends, and noted that claims 6 and 15 are unclear as they could be

interpreted to read on a cell in a human.

As amended, the claims no longer recite the term "derived from," claim 14 is in independent form, and claims 6 and 15 are now directed to "isolated" cells. Applicants submit that these amendments overcome the § 112, second paragraph, rejections and respectfully request reconsideration and withdrawal of this basis for rejection.

VI. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 5-6, 8-15, and 17 were rejected under 35 § U.S.C. 112, first paragraph, on the basis that the disclosure in Applicants' specification (1) fails to provide a written description of the claimed invention and (2) is not commensurate in scope with the claimed invention. For the following reasons, these rejections may be withdrawn.

Written Description

The Office rejected claims 5-6, 8-15, and 17 under 35 U.S.C. § 112, first paragraph, based on the assertion that the claims contain subject matter which was not described in the specification in such a way as to convey possession of the claimed invention. In particular, the Office asserted (page 4):

> The claims are drawn to a limitless number of fusion constructs comprising the vector composition being claimed. In addition claim 17 is drawn to a limitless number of ligands ... The specification does not provide an adequate disclosure of species that fall within the claimed genera of domains or ligands, such that a skilled artisan would be able to distinguish amongst those that fall within the claims from

those that fall without.

Applicants respectfully disagree.

The statutory language of 35 U.S.C. § 112, first paragraph, in issue, states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ...

The legal standard for sufficiency of a patent application's written description is whether that description "'. . . reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter.'" *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983))); *Fiers v. Revel*, 984 F.2d 1164, 1170 (Fed. Cir. 1993) (citation omitted).

Claim 5, as amended, reads:

> A vector comprising a gene encoding a fusion protein comprising (a) a first polypeptide and (b) a second polypeptide, wherein said first polypeptide comprises a ligand binding domain of a steroid hormone receptor that, upon ligand binding, dimerizes, and wherein said second polypeptide comprises a cytokine receptor or a proliferation-inducing part thereof that, upon said dimerization of said first polypeptide, imparts proliferation activity to a cell.

And claim 8 is directed to a vector that includes a desired exogenous gene and a gene encoding a fusion protein having the features of the fusion protein of claim 5. Claim 14

is directed to a vector system that includes a first vector containing a desired exogenous gene and a second vector containing a gene encoding a fusion protein having the features of the fusion protein of claim 5, where the gene encoding a fusion protein and the exogenous gene are located on separate molecules. Claim 17 is directed to a kit which includes the vector of claim 5 or 8 and a steroid hormone ligand capable of acting on the ligand-binding domain of the fusion protein encodes by the gene contained in the vector. Exemplary kits are described, for instance, at page 5, line 27, to page 6, line 1, of the specification.

Applicants' specification conveys, with reasonable clarity to the skilled persons, that the inventors possessed the presently claimed invention. First, Applicants' specification unmistakably informs the skilled person of the fusion protein encoded by the claimed vector includes both a steroid hormone receptor polypeptide and a cytokine receptor polypeptide. For example, as filed, the specification at page 3 (lines 20-25) states:

> [T]he present inventors have thought of constructing a chimeric gene between the G-CSF receptor gene and the estrogen receptor gene, introducing the chimeric gene into cells, and externally stimulating the cells by estrogen to forcibly dimerize the G-CSF receptor portion of the chimeric gene product [a fusion protein].

Next, the specification at page 4 (lines 3-6), in describing the requisite domains of the fusion protein, states:

> The present invention relates to a fusion protein comprising a ligand-binding domain, a domain that associates when a ligand

> binds to the ligand-binding domain, and a domain that imparts proliferation activity to a cell upon association.

Further, with respect to a ligand-binding domain of the fusion protein, which further includes a dimerization domain, and the ligands themselves, the specification at page 6, lines 2-7, states:

> Any ligand can be used in the present invention as long as it acts on a specific protein to cause association of the protein, but a steroid hormone is preferable. Examples of the steroid hormone include estrogens, androgens, progesterone, glucocorticoids, and mineral corticoids. They are used in combination with their respective receptor proteins.

While, with respect to the cytokine receptor portion of the fusion protein, the specification, at page 6, lines 7-12, states:

> Any cytokine receptor can also be used in the present invention as long as it imparts proliferation activity to a cell upon association. Examples of the cytokine receptor are those belonging to the cytokine receptor family including G-CSF and those belonging to the tyrosine receptor family including c-kit and flk2/flt3.

And with respect to the proliferation-inducing domain of the cytokine receptor, the specification at page 6, lines 13-18, states:

> As the "domain which imparts proliferation activity to a cell" of the fusion protein according to the present invention, it is possible to use a molecule that transmits the intracellular proliferation signal, for example, an entire molecule of a cytokine receptor. It is also possible to use only a domain in the molecule that imparts proliferating activity to a cell.

Given these passages of Applicants' specification alone, there can be no doubt that

Applicants have satisfied the written description requirement, and that Applicants have unambiguously described their invention so as to reasonably convey to persons skilled in the art that the inventors possessed the subject matter in question.

In addition to the aforementioned description, Applicants' specification, as filed, further describes several different steroid hormone receptor:cytokine receptor fusion proteins. Exemplary fusion proteins are described in Figure 1, and at page 7, line 22, to page 8, line 2, which states:

> Fig. 1 (A) shows a chimeric molecule between the G-CSF receptor and the estrogen receptor (GCRER). (B) shows a mutant of the chimeric molecule between the G-CSF receptor and the estrogen receptor, deficient in the 5th through 195th amino acids of the G-CSF receptor (GCR Δ (5-195)/ER). (C) shows a mutant of the chimeric molecule between the G-CSF receptor and the estrogen receptor, deficient in the 5th through 195th amino acids and the 725th through 756th amino acids of the G-CSF receptor (GCR Δ (5-195, 725-756/ER).

Furthermore, Applicants note that their specification, for example, at page 9, lines 12-16, describes exemplary methods for engineering nucleic acid molecules to generate sequences that express the presently claimed fusion proteins. In particular, the specification states:

> In order to produce a chimeric protein comprising the entire G-CSF receptor and the ligand (estrogen)-binding domain of the estrogen receptor (hereafter designated simply as "GCRER"), the fusion gene having cDNAs that encode the respective proteins (Fig. 1(A)) was constructed.

And, for example, at page 10, lines 1-2, the specification describes exemplary vectors

containing genes expressing a presently claimed fusion protein. Here, the specification states:

> The three kinds of selective amplification genes prepared in Example 1 were introduced into plasmid "pCMX."

In addition, the written description rejection is without merit as it relates to the claims that depend from claim 8. For example, claims 10 and 12, which each depend from claim 8, respectively limit the cytokine receptor to the G-CSF receptor and the steroid hormone receptor to the estrogen receptor. Accordingly, the genus recited in claims 10 and 12 is less broad and variable, and, therefore, Applicants submit that the working examples disclosed in their specification are sufficiently representative to demonstrate that Applicants were in possession of the claimed genus at the time the present application was filed. (Claims 9, 11, and 13 have been canceled and, therefore, the rejection of these claims is moot.)

Evidence in the scientific literature also plainly further supports Applicants' position that the disclosed exemplary estrogen and G-CSF receptors are representative of steroid hormone and cytokine receptors respectively. For example, Applicants' exemplary estrogen receptor is representative of steroid hormone receptors. As evidence of this assertion, Applicants direct the Office's attention to Thornton ("Evolution of vertebrate steroid receptors from an ancestral estrogen receptor by ligand exploitation and serial genome expansions." *Proc. Natl. Acad. Sci. U.S.A.* 98:5671-5676, 2001; copy enclosed). As is evident from the title, steroid receptors evolved from an ancestral

estrogen receptor, and given this evolutionary connection, biological similarities are known to exist in this conserved receptor family.

In addition, Applicants' exemplary G-CSF receptor is representative of cytokine receptors. Indeed, no substantial variation exists, with respect to a proliferation–inducing domain, within the family of cytokine receptors. First, the cytoplasmic region of the G-CSF receptor is known in the art to have a membrane-proximal domain, which has two conserved subdomains designated box 1 and box 2. The membrane-proximal domain is known to be a binding site for the Jak family of tyrosine kinases and is essential for mitogenic signaling (see, for example, page 381, col. 2, Omura et al. ("Acceleration of granulocyte colony-stimulating factor-induced neutrophilic nuclear lobulation by overexpression of Lyn tyrosine kinase." *Eur. J. Biochem.* 269: 381-389, 2002); copy enclosed).

Furthermore, the membrane-proximal domain that includes the box1/box2 motif is well conserved among cytokine receptor family members. As evidence of this assertion, Applicants direct the Office's attention to Ihle ("Cytokine receptor signaling." *Nature*, 377:591-594, 1995; copy enclosed) and Murakami et al. ("Critical cytoplasmic region of the interleukin 6 signal transducer gp 130 is conserved in the cytokine receptor family." *Proc. Natl. Acad. Sci. USA*, 88:11349-11353, 1991; copy enclosed). In particular, Applicants direct the Office's attention to Figure 2 and Figure 1B of Ihle and Murakami, respectively. Further, the extracellular region of the G-CSF receptor includes a four

cysteine region and a Ws x Ws box that are conserved among other cytokine receptors such as those of IL-2, -3, -4, -6, -7, GM-CSF, and erythropoietin receptors (see, e.g., Bazan, "Structural design and molecular evolution of a cytokine receptor superfamily." *Proc. Natl. Acad. Sci. USA,* 87:6934-6938, 1990; copy enclosed).

In addition to the G-CSF receptor, it has been shown that this membrane-proximal region comprising box1/box 2 is vital for cell proliferation signal transduction in a variety of cytokine receptors such as IL-6R (gp 130) and IL-2R (see, Murakami et al.) and the EPO receptor (see Ihle, for example, Fig. 1). Therefore, as there is no substantial variation among cytokine receptors with regard to the domain required for transducing the proliferation signal, Applicants' description and examples utilizing the G-CSF receptor are plainly representative of cytokine receptors.

Furthermore, as cytokine receptors were well studied, at the time of filing the instant application, a skilled artisan could routinely isolate a proliferation-inducing domain of a cytokine receptor without undue experimentation.

Applicants further note that cytokine receptors, like the G-CSF receptor, share additional characteristics recognizable by one skilled in the art. For example, cytokine receptors, like the G-CSF receptor, dimerize when activated. Indeed, as noted by Heldin, ("Dimerization of cell surface receptors in signal transduction." Cell 80:213-223, 1995; copy enclosed), at page 213, col. 1, "Growth factors and cytokines exert their effects via binding to cell surface receptors...such receptors often are activated by ligand-induced

dimerization or oligomerization." (see Heldin et al., Abstract, lines 5 to 8) . In addition, Alexander et al. ("Point mutations within a dimer interface homology domain of c-Mpl induce constitutive receptor activity and tumorigenicity." The EMBO Journal 14:5569-5578, 1995; copy enclosed) at page 5569, abstract, describe that "[a] recurring mechanism for the activation of haemopoietin receptors is the formation of functional complexes by receptor subunit oligomerization."

Applicants also point out that the G-CSF receptor belongs to the Class I cytokine receptor family, which is the larger of the two cytokine receptor families (see, for example, Heldin et al., Table 1, page 214). The structural features of the Class I cytokine receptor family, known when Applicants filed their application, are disclosed in detail on page 216, under "Cytokine receptors."

In sum, Applicants' specification plainly meets the written description standard by providing not only clear language describing the claimed fusion proteins, but also by describing several working examples of fusion proteins. This description, which is beyond dispute, would be recognized by one skilled in the art. Moreover, Applicants have, from the time they originally filed this application, claimed this type of fusion protein as part of their invention. One skilled in the art therefore certainly would recognize that, at the time of filing, the inventors were in possession of such claimed fusion proteins. The written description requirement of § 112, first paragraph has been satisfied by Applicants, and the rejection of claims 5-6, 8-15, and 17 should be

withdrawn.

Enablement

The Office also rejected claims 5-6, 8-15, and 17 under 35 U.S.C. § 112, first paragraph, for an asserted lack of enablement. The Office stated (page 6, page 7):

> The invention is drawn to three separate domains each with a particular function. Within each domain there is a virtually limitless number of possible constructs. In addition, the invention is drawn to gene therapy, which can involve complex multi-factorial pathways in the body.

With regard to the unpredictability of the art, the Office asserted (page 7, page 8):

> [T]he fusion proteins encoded on the vector constructs, when expressed in the cell or in the body may be toxic to the cell or host ... Furthermore, one or more of the domains encoded on the vector may function inadequately or not at all.
>
> * * *
>
> [G]ene therapy is a highly unpredictable art with poor efficiency of delivery of the transgene to the target cells, poor transformation efficiency of target cells, unpredictable and transient expression of the transgene in target cells.

Applicants respectfully disagree.

Applicants note that the test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). Those skilled in the art

routinely screen many fusion proteins in order to isolate a fusion protein having the desired effect; such screening is routine in the art and does not constitute undue experimentation.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. As the Office correctly notes, there are many factors to be considered when determining whether the specification is enabled and whether any necessary experimentation is "undue." These factors include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention. Applicants respectfully submit that one skilled in the art would not have to use undue experimentation to make and use the invention within the scope of the amended claims.

In this case, the state of the prior art and the level of ordinary skill is such that the production of a protein from a gene construct, or a vector containing such a gene, is merely routine. A fusion gene implicitly and inherently describes and enables its corresponding fusion protein. Any degree of unpredictability is counterbalanced by the fact that the present specification not only provides a high level of explicit direction as to

how to make and use fusion proteins within the scope of the claims from the exemplary fusion genes but also provide a number of working examples of fusion genes and their corresponding fusion proteins.

The Office alleged that one or more of the domains may function inadequately or not at all. However, Applicants set forth a series of representative working examples that suggest the contrary. For instance, in Example 2, Applicants describe the transfection of Ba/F3 cells with a number of GCRER constructs. Similarly, in Example 6, Applicants describe the transfection of bone marrow cells with similar GCRER constructs. As a result of transfection, these cells produced fusion proteins commensurate with the pending claims. Furthermore, Applicants not only confirmed expression of the fusion proteins, but also confirmed the fusion proteins to be active. Specifically, all the transfected cells demonstrated estrogen-dependent proliferation, confirming that the activity of fusion protein domains was not affected. Thus, the specification clearly teaches that functional, active fusion constructs commensurate with the scope of the claims may be constructed from the disclosures in the patent coupled with information known in the art without undue experimentation.

The Office further asserted that the resulting proteins may lose activity or be toxic to the host cell. On this point, Applicants submit, in light of the successes documented in the examples provided in the specification, that there is simply no reason to expect the resulting proteins to be inactive or toxic. For example, as discussed in Examples 2 and 6,

none of the cells transfected with the various chimeric GCRER plasmids (i.e., cells producing various GCRER fusion proteins) suffered any negative consequences.

While the Office cited several references in support of the assertion that gene therapy is still a highly unpredictable art within biology and medicine (Cheok, Nature 421:678, 2003; Juengst, BMJ 326:1410-1411, 2003; Kmiec, American Scientist 87:240-247, 1999; Anderson, Nature 392:25-30, 1998; and Verma and Somia, Nature 389:239-242, 1997), Applicants note that the Federal Circuit has long held that it is not necessary for all possible embodiments of a claim to be operative in order for that claim to be enabled. *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). The proper test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation. The fact that certain risks and inefficiencies remain is not dispositive of the issue of enablement.

In this regard, Applicants also submit that the Office's concerns regarding the "unpredictability" of the field of gene therapy appear to be in conflict with the art cited by the Office as anticipating the claimed invention (Littlewood et al., Nucleic Acids Research 23:1686-1690, 1995; "Littlewood;" Roussel et al., Proc. Natl. Acad. Sci. USA 85:5903-5907, 1988; "Roussel;" Greenberg et al., U.S. Patent Number 5,747,292; "the '292 patent;" Roberts, U.S. Patent Number 5,686,281; "the '281 patent;" and O'Malley et

al., U.S. Patent Number 6,416,998; "the '998 patent") which demonstrate the utility and operability of a variety of chimeric receptors. For instance, the '281 patent, in Example 10, teaches that T cells expressing zeta-based and CD28-based chimeric receptors function *in vivo*. These successes further support the feasibility of *in vivo* gene therapy.

Moreover, Applicants note that the specification is presumed to be in compliance with the enablement requirement of 112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. In a situation in which the Patent Office questions the enablement of a claim, the C.C.P.A. has stated (*In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971):

> [I]t is incumbent upon the Patent Office ... to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

In this case, the Office has failed to adequately support its assertion that the vectors of the pending claims would be inoperable *in vivo*, particularly in light of Applicants' *in vitro* successes and the accomplishments of others in the relevant art. Although the invention is at an early stage in development, the experimentation needed to put the invention into practice is well within ordinary skill and would be considered to be routine. Accordingly, one reasonably skilled in the art would be able to make and use the full scope of the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Finally, Applicants note that the Federal Circuit recently stated that "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *In re Brana*, 51 F.3d 1560, 1568, 34 U.S.P.Q.2d 1437, 1442 (Fed. Cir. 1995). The fact that further experimentation may be needed to optimize the efficacy and/or efficiency of the claimed vectors *in vivo* does not in itself negate enablement. Furthermore, under the current case law, clinical efficacy is not required to show that a therapeutic process has utility (M.P.E.P. § 2107 Eighth Edition, Rev. 1, February 2003). As stated in § 2107.01 of the M.P.E.P., "courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a therapeutic regimen" or that a therapeutic treatment regimen is not at a stage where it is ready to be practiced on humans. *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). It is not within the province of the U.S.P.T.O. to require proof of efficacy in humans to grant a patent whose claims encompass therapeutic methods. The U.S.P.T.O. guidelines are explicit on this point: "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders" (M.P.E.P. § 2107.03, Eighth Edition, Rev. 1, February 2003).

For all the reasons set forth above, Applicants' specification clearly enables a skilled artisan to make and use the vectors recited in the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection in light of the above comments.

VII. Rejections Under 35 U.S.C. § 102

The Office cited several references as anticipating the presently claimed invention (Littlewood et al., Nucleic Acids Research 23:1686-1690, 1995; Roussel et al., Proc. Natl. Acad. Sci. USA 85:5903-5907, 1988; Greenberg et al., U.S. Patent Number 5,747,292; Roberts, U.S. Patent Number 5,686,281; and O'Malley et al., U.S. Patent Number 6,416,998). Anticipation requires that each and every element of the claim be disclosed in the prior art. As applied to the amended claims, these rejections should be withdrawn.

Littlewood:

Claims 5-6, 8, 11-13, and 15 were rejected under 35 U.S.C. § 102(a) as being anticipated by Littlewood. Applicants have amended the claims to require that the vector includes a gene encoding a fusion protein that contains a ligand-binding domain of a steroid hormone receptor and a cytokine receptor or a proliferation-inducing part thereof. Because Littlewood fails to disclose a gene encoding such a fusion protein, it cannot anticipate the claims as amended. Furthermore, Applicants note that c-Myc is a

transcription factor, not a cytokine. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Roussel:

Claims 5 and 6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Roussel. Applicants note that the claims, as amended, require that the gene encodes a fusion protein containing a ligand-binding domain of a steroid hormone receptor and a cytokine receptor or a proliferation-inducing part thereof. Roussel nowhere teaches a fusion protein that includes a ligand-binding domain of a steroid hormone receptor. Thus, the Roussel reference fails anticipate the claims.

The '292 patent:

Claims 5-6, 8-10, 13, and 15 were rejected under 35 U.S.C. § 102(e) as being anticipated by Greenberg et al. (U.S. Patent Number 5,747,292; "the '292 patent"). Again, Applicants note that the present claims require that the vector includes a gene encoding a fusion protein containing a ligand-binding domain of a steroid hormone receptor and a cytokine receptor or a proliferation-inducing part thereof. Such a gene is nowhere taught by Greenberg. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

The '281 patent:

Claims 5, 6, 8-10, and 15 were rejected under 35 U.S.C. § 102(e) as being anticipated by Roberts (U.S. Patent Number 5,686,281; "the '281 patent"). In particular, the Office asserted (page 12):

> The '281 patent teaches DNA constructs encoding chimeric (i.e. fusion) proteins comprising at least three domains in a single chain molecule: a ligand-binding domain, a transmembrane (i.e. associative) domain and a cytoplasmic co-stimulatory effector function-signaling domain (i.e. proliferation) ... Furthermore, the proliferative domain is a cytokine - CD28. (column and line numbers omitted)

As an initial matter, Applicants submit that the claims, as amended, are free of this basis for rejection. As noted above, to anticipate a claim, a reference must disclose each and every element of the claim. The present claims require the claimed vector to include a gene that encodes a fusion protein containing the ligand-binding domain of a steroid hormone receptor and a cytokine receptor or a proliferation-inducing part thereof. The '281 patent fails to disclose a gene encoding a fusion protein having each and every feature required by the claim. Accordingly, Applicants submit that the '281 patent cannot anticipate the present claims. The § 102 rejection over this reference should be withdrawn.

With respect to the cytokine receptor portion of the claimed fusion protein, the Office pointed to column 13, lines 34-45 of the '281 patent and characterized CD28 as a cytokine. Applicants submit that, to the extent that CD28 was characterized as a

cytokine, the Office was in error. The section of the '281 patent referred to by the Office simply teaches that CD28 can affect cytokine production. In particular, the '281 patent teaches (column 13, lines 39-46):

> One measure of T cell activation is the production of cytokines. This is true for both CD4 and CD8 T cells. Moreover, cytokine production is susceptible to anergy when T cells are stimulated via the TCR without co-stimulation through CD28. Another aspect of CD28 co-stimulation is its ability to augment cytokine production by increasing transcription of cytokine genes and stabilizing cytokine mRNAs.

CD 28 is not a cytokine receptor. As is taught in Applicants' specification, examples of cytokine receptors include G-CSF, c-kit, and flk2/flt3 (see, e.g., page 6, lines 7-12).

Further, with respect to G-CSF, Applicants submit that the section of the '281 patent cited by the Office, contrary to the Office's assertion, does not teach that the "chimeric receptors can include G-CSF." In fact, this section teaches (column 14, lines 54-63):

> Additional types of cells that would benefit from the introduction of the chimeric receptors of the invention include cells that have genes previously introduced or simultaneously introduced **with** a chimeric receptor which may serve in protein production or to correct a genetic defect. Production of proteins may include growth factors, such as, erythropoeitin, G-CSF, M-CSF, and GM-CSF, epidermal growth factor, platelet derived growth factor, human growth factor, transforming growth factor, etc; lymphokines, such as interleukins. (emphasis added)

Clearly, this section of the '281 patent refers to genes that are separate from a gene

encoding a chimeric receptor and also fails to teach a fusion protein having a cytokine receptor portion.

The '998 patent:

Claims 5-6, 8, and 11-15 were rejected under 35 U.S.C. § 102(e) as being anticipated by O'Malley et al. (U.S. Patent Number 6,416,998; "the '998 patent"). As noted above, the present claims feature a gene encoding a fusion protein containing a steroid hormone receptor and a cytokine receptor or a proliferation-inducing part thereof. O'Malley fails to disclose a gene encoding a fusion protein containing a steroid hormone receptor and a cytokine receptor or a proliferation-inducing part thereof. Thus, this reference cannot anticipate the claims as amended and this rejection should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance and this action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three months, to and including May 26, 2004, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 26 May 2004

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